REMARKS

Claims 49-61, 63-66, 68-70, and 72 are pending in the case. No amendments have been made to the instant pending claims. Claims 73-75 have been added. Support for the claims can be found throughout the specification, for example on page 37, lines 28-33. The claims contain no new matter. After entry of the amendment, claims 49-61, 63-66, 68-70, and 72-75 will be pending.

Rejection of claims for anticipation under 35 U.S.C. §103(a)

Isner and Hammond

All of the claims pending in the case prior to the amendment are rejected as being unpatentable over Isner (WO 97/14307, hereinafter Isner) in view of Hammond et al. (US Patent 5,880,099, hereinafter Hammond) for essentially the reasons stated in the previous Office Actions. The Office Action states that:

> [I]t would have been obvious for an ordinary skilled artisan to modify the method of Isner by further administering to the treated mammal an effective amount of GM-CSF or an effective fragment thereof in light of the teachings of Hammond et al. and since Isner also teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance activity of targeted cells, including nitric oxide synthase which is also an angiogenic protein or factor (page 11, lines 15-19; and page 7, lines 16-24). (Office Action at page 4)

Applicant respectfully disagrees.

The Applicant submits that the Examiner is not considering the Isner reference as a whole. Particularly, the rejection does not take into consideration an essential element of the teachings of Isner of administration of the ***angiogenic agent directly to the ischemic tissue***. When taken as a whole, modification of Isner to include systemic administration, as taught by Hammond, would change the principle of operation of Isner; therefore, the references cannot be combined and the methods claimed in the instant application cannot be *prima facie* obvious in view of the cited references.

MPEP (Section 2141.02 (VI)) states:

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) (Claims were directed to a process of producing a porous article by expanding shaped, unsintered, highly crystalline poly(tetrafluoroethylene) (PTFE) by stretching said PTFE at a 10% per second rate to more than five times the original length. The prior art teachings with regard to unsintered PTFE indicated the material does not respond to conventional plastics processing, and the material should be stretched slowly. A reference teaching rapid stretching of conventional plastic polypropylene with reduced crystallinity combined with a reference teaching stretching unsintered PTFE would not suggest rapid stretching of highly crystalline PTFE, in light of the disclosures in the art that teach away from the invention, i.e., that the conventional polypropylene should have reduced crystallinity before stretching, and that PTFE should be stretched slowly.).

Isner teaches "a method for treating ***ischemic tissue*** in a mammal which comprises ***injecting said tissue*** with an effective amount of a nucleic acid capable of expressing an angiogenic protein" (See Abstract). The delivery of agents ***to ischemic tissue*** is an essential element of Isner. Systemic administration of agents, as suggested by Hammond, changes the essential nature of the invention of Isner. Therefore, the combination of references cannot be proper.

The invention of Isner was made to overcome limitations in the prior art regarding the limitation of treatment methods which require the repeated doses of angiogenic proteins by intramuscular administration over a range of 10 to 14 days. "Thus, one major limitation of recombinant protein therapy is its potential requirement to maintain an optimally ***high and local concentration*** over time" (page 1, lines 19-21) Systemic administration was clearly known at the time of the filing of the Isner application, however, systemic administration of agents presumably was insufficient to provide the ***high and local concentration*** of angiogenic agents

over time that was required for the treatment of ischemia. Therefore, Isner must be understood as teaching away from systemic administration of angiogenic agents.

The Summary of the Invention of Isner clearly demonstrates that injection of therapeutics into the ischemic tissue is an essential element of the invention. For example,

"nucleic acid... capable of expressing an angiogenic protein... ***when injected into an ischemic tissue*** induces angiogenesis, providing the ischemic tissue with increased blood vessels." (page 4, lines 5-9)

"a method for ***treating ischemic tissue*** in a mammal which comprises ***injecting said tissue*** with an effective amount of a nucleic acid capable of expressing an angiogenic protein." (page 4, lines 13-16)

"The ***ischemic tissue may be injected*** with the nucleic acid by any injection means." (page 4, lines 25-26)

Therefore, it is clear that the method requires that the ***injection of the nucleic acid into the ischemic tissue***.

Isner further teaches that the angiogenic protein to be encoded by the nucleic acid can include colony stimulating factor or macrophage colony stimulating factor. According to the invention, ***angiogenic proteins must be injected into the ischemic tissue***.

The Office Action refers to two sections of the specification that allegedly provide teachings regarding the use of any of a number of angiogenic proteins. For example, the Office Action points to page 7, lines 16-24. Proteins defined as angiogenic proteins are listed. Reading the paragraph in context, the first sentence states, "The nucleic acid may be any nucleic acid...." The method of administration of the nucleic acid is provided in the previous paragraph which states:

> The present invention provides a method for ***treating ischemic tissue*** in a mammal which comprises ***injecting said tissue*** with an effective amount of a nucleic acid encoding an ***angiogenic protein*** operably linked to a promoter

(nucleic acid cassette) to result in expression of a protein ***when delivered to ischemic tissue***.

The portion of the specification indicated by the Examiner on page 11 also provides no teaching or suggestion for administration of an angiogenic agent should be any place other than to the ischemic tissue.

Therefore, upon reading Isner, one skilled in the art would conclude that administration of a nucleic acid to an ischemic tissue overcomes the limitation of the prior art which taught repeated administration of protein. As systemic administration was well known at the time; however, successful treatment of ischemic injury or disease required ***administration to the ischemic tissue***, as noted in the background section. One skilled in the art would conclude that systemic administration of angiogenic proteins did not produce the desired result or was not effective in the treatment of ischemic tissue. Delivery of the nucleic acid ***directly to the ischemic tissue*** is an essential principle of the operation of the invention of Isner.

Isner cannot be properly modified to include delivery of an angiogenic nucleic acid to a site remote from the ischemic tissue, or be properly combined with a reference that exclusively teaches administration of an agent systemically.

MPEP section 2143.01(VI) states:

> If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (Claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. Patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection holding the "suggested combination of references would require a

> substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.).

Combination of Isner with Hammond would require a change in the basic principle upon which the method of Isner relies. The principle requires injection of the nucleic acid encoding the angiogenic agent directly to the ischemic tissue. Moreover, Isner teaches the use of nucleic acid expression vectors to provide sustained release of angiogenic proteins as the repeated administration of proteins is undesirable. Therefore, it would not be obvious to combine Isner with a reference that teaches administration of proteins that are likely liable and would require repeated administration. Furthermore, the one example of Hammond that teaches systemic administration pf GM-CSF provides results which are inconclusive at best (Example 3). Therefore, the result would not motivate one to modify the method of Isner by administration of systemic GM-CSF. Applicant submits that Isner cannot be properly modified or combined with Hammond to make the teachings of the instant invention obvious.

The Office Action alleges that Hammond teaches that:

> cytokines such as stem cell factor (SCF), granulocyte-macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF) <u>are capable of mobilizing bone marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient</u> (see at least Summary of the Invention). Hammond et al further note that <u>CD34+ circulating cells in the blood can participate in the repair of ischemic tissue</u> (col. 3, lines 28-37). (At page 4, underline in original)

Again, one must look at the Hammond reference as a whole for what the reference actually teaches. Specifically, the Examples must be analyzed to determine what one skilled in the art would conclude from the reference.

The Office Action states that the previous comments of the Applicant regarding

> the many types of cells capable of releasing a variety of growth factors that may have contributed to the observed increase in endothelialization… is irrelevant because neither the present invention nor the modified method based on the combined teachings of Isner and Hammond as set forth above requires seeding of BMB and/or transplantation of bone marrow blood (BMB).

Therefore, according to the Office Action, Examples 1 and 2 provide no motivation to combine the references. Applicant agrees that Examples 1 and 2 provide no teachings relevant to the instantly claimed method for at least the following reasons.

In Example 1, whole bone marrow is used in the method. Bone marrow is a complex and dynamic mixture of cells that secrete a number of known and unknown factors. Therefore, one cannot attribute the results observed to the presence or absence of any single factor or that the markers observed on the cells at the time of collection from the bone, upon delivery to the artificial vasculature, and upon analysis after days or weeks in culture would be consistently present. Hammonds conclusion that "it seems likely" that CD34+ cells were involved in the endothelialization observed" (col 8, lines 14-16) is equivocal at best. Hammond acknowledges that it would be inappropriate to attribute the results seen purely to the CD34+ cells. Specifically, Hammond states:

> It should be noted further that the BMB used for seeding also contained many types of cells that are capable of releasing a variety of growth factors that may have contributed to the observed endothelization, e.g., dendritic cells, megacaryocytes, macrophages, and lymphocytes.

It is noted that Hammond performed immunohistochemical staining for only three markers, FVIII/vWF an endothelial marker which stains new blood vessels, CD34 also a marker for endothelial cells, and α-actin a marker for smooth muscle cells. (col 6, lines 51-56) Blood vessels have both endothelial cells and smooth muscle cells. The presence of the cell-type specific markers in the vasculature ***after*** formation does not mean that the markers were present in the cells when the bone marrow was applied, i.e. ***before*** the formation of the vasculature. In

fact, it would be surprising if the repeated rounds of clotting, pressurization of the graft, and exposure of the graft to heparin would not alter protein expression in the cells.

Furthermore, Hammond teaches an *ex vivo* procedure wherein BMB is applied and clotted repeatedly on the graft. Such a density of cells could not reasonably be achieved *in vivo* gathering bone marrow cells from circulation to mimic the graft coated *ex vivo*. The ability of a cell to adhere to a newly forming vessel *in vivo* cannot be predicted from experiments performed by coating an artificial vessel with bone marrow cells *ex vivo*.

Moreover, the bone marrow blood coated grafts showed "undesirable side effects" (col 7, line 61) after 5 weeks including the presence of osteoblasts, osteocytes, and microcalcifications. Therefore, one skilled in the art would not be motivated to attempt to use whole bone marrow to promote angiogenesis or endothelialization of grafts.

Example 2 teaches that endothelialization of grafts can occur without any intervention and that the cells are provided by bone marrow of the graft recipient. As in Example 1, bone marrow is a complex mixture of cells. Moreover, the example teaches that endothelialization occurs in the absence of added bone marrow, cytokines, or other growth factors. The Example can provide no teaching or suggestion regarding agents that would promote or suppress angiogenesis.

Example 3 allegedly teaches that "G-CSF or other agents capable of mobilizing bone marrow is a promising avenue for promoting healing of vascular grafts." This conclusion suspect, at best. Two dogs in the control group showed graft surfaces 20-30% covered with ECL. Dogs that received G-CSF showed graft surfaces that were 35% or 80% covered with ECL. One skilled in the art would question how meaningful these data are. Due to the small numbers in the group and the large variation within the group, it is unlikely that there is a statistical difference between the groups. Is 35% endothelialization the "real" result, or is 80% endothelialization the "real" result? One unbiased and skilled in the art would conclude that further experiments might be warranted, but that no conclusions could be drawn from such a (poorly designed) experiment.

The data could also suggest that a more complex mixture of bone marrow cells need to be mobilized to promote endothelialization as was seen when whole bone marrow was used. The statement in the Office Action that "Hammond also notes that CD34+ circulating cells in blood can participate in the repair of ischemic tissue." However, the data strongly suggest that CD34+ cells at best are participants, and that the mobilization of CD34+ cells might promote increased endothelialization under the appropriate circumstances. The fact that a cell type can be used in a process does not mean that it is useful alone in the absence of appropriate co-factors or cells. Wooden boards can be used to build a house, but in the absence of nails or tools, one cannot build a house. Enrichment of a single component in a process that requires multiple components is not necessarily useful for the process.

Further, the indication of the claim that "GM-CSF is sufficient for increasing the concentration of bone marrow-derived endothelial progenitors in a recipient of a synthetic vascular graft" does not demonstrate that such cells increase angiogenesis in ischemic tissue, or even increase endothelialization in a graft. According to the claim, both dogs that received GM-CSF should have had an increase in the number of endothelial progenitor cells in circulation. An increase in endothelialization relative to control was seen in one dog, and not in the other. Therefore an increased number of endothelial progenitors does not reliably result in an increase in endothlialization. Similarly, it would not be expected that an increase in endothelial progenitor cells would reliably result in an increase in angiogenesis.

Examples 4 and 5 are prophetic and use the method of Example 1 to coat the graft with bone marrow.

If any conclusion can be drawn from Hammond in view of Isner, one may conclude that the systemic administration of angiogenic agents does not consistently work, and is a reason for the inconclusive, and therefore failed experiment. In fact, Hammond could be seen as confirming the teachings of Isner that administration to the site of desired angiogenesis is essential. Providing a ***high and local concentration*** of angiogenic agents and other growth factors, as would be provided by the bone marrow coated graft, angiogenesis is promoted. Systemic administration fails to provide the ***high and local concentration*** of factors required, therefore it fails to consistently produce the desired result.

One would not be motivated to modify the methods of Isner that produce consistently statistically significant, desirable results to incorporate the method of Hammond based on the dubious results of a single experiment. The data of Hammond cannot provide a reasonable expectation of success in modification of a different method as one skilled in the art would not consider that the experiment set forth in Example 3 was successful, or that the results of further experimentation could be predicted based on the inconclusive results.

MPEP Section 2143.01(III) states:

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007)("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

The result of a repeat of the experiment of Example 3 of Hammond is not predictable. Therefore, the results from an experiment based on the experiment in Example 3 cannot be predictable.

Therefore the combination of references cannot be proper.

Delivery of an angiogenic agent to a site ***other than the ischemic tissue*** would require a change in the principle of operation of the method of Isner. The local delivery of bone marrow in Hammond is a mixture of undefined factors that cannot make the instant claims obvious. Therefore, the combination of references cannot be proper.

Withdrawal of the rejection of claims 49-61, 63-66, 68-70, and 72 for obviousness over Isner in view of Hammond is respectfully requested.

Applicant submits that newly added claims 73-75 are also not obvious over Isner in view of Hammond at least for the reasons set forth above.

Isner and Bussolino

All of the claims pending in the case prior to the amendment are rejected as being unpatentable over Isner in view of Bussolino et al. (hereinafter Bussolino) for essentially the reasons stated in the previous Office Actions. The Office Action states that:

> [I]t would have been obvious for an ordinary skilled artisan to modify the method of Isner by utilizing recombinant G-CSF and /or GM-CSF as an endothelial cell mitogen to be administered to a patient in need thereof in light of the teachings of Bussolino et al., and since Isner also teaches that an angiogenic factor can be combined with other genes or other encoded gene products to enhance the activity of the targeted cell, including nitric oxide synthase which is also an angiogenic protein or factor (page 11, lines 15-19, and page 7, lines 16-24).

Applicant respectfully disagrees.

As discussed above, an essential element of the teachings of Isner of administration of the ***angiogenic agent directly to the ischemic tissue***. When taken as a whole, modification of Isner to include systemic administration would change the principle of operation of Isner.

For the reasons set forth above, upon reading Isner, one skilled in the art would conclude that administration of a nucleic acid to an ischemic tissue overcomes the limitation of the prior art which taught repeated administration of protein. As systemic administration was well known at the time; however, successful treatment of ischemic injury or disease required ***administration to the ischemic tissue***, as noted in the background section. One skilled in the art would conclude that systemic administration of angiogenic proteins did not produce the desired result or was not effective in the treatment of ischemic tissue. Delivery of the nucleic acid directly to the ischemic tissue to achieve a ***high and local concentration*** of angiogenic factors is an essential principle of the operation of the invention of Isner. Moreover, Isner demonstrates that delivery of a nucleic acid directly to the ischemic tissue results in consistent and robust angiogenesis;

therefore, one would not be motivated to rely on the teachings of Bussolino which concludes that the results presented in the reference are inconclusive.

The equivocal statements regarding the meaning of the data in the Bussolino reference would not suggest reliance on the reference regarding the activity of G-CSF or GM-CSF with FGF. Specifically, in the right hand column of page 994, Bussolino states:

> The cooperative angiogenic activity of G-CSF and bFGF was evident in terms of response intensity (number of capillaries, number of positive implants, time to reach the pellets). ***This initial observation needs to be extended***. However, the cooperative effect of G-CSF and bFGF in inducing in vivo angiogenesis was somewhat ***surprising*** and intriguing. In fact, in vitro, in spite efforts involving different experimental designs only one of which is shown here (see Results), we have found ***no indication of a synergistic action*** of these two cytokines on HUVEC proliferation and migration. ***At best, an additive effect was observed***. In vivo angiogenesis occurs as the endpoint of complex interactions between many events involving remodeling of the extracellular matrix and the release of several "factors" (12, 50). This apparent ***paradox*** of a combination of cytokines acting directly on endothelial cells, showing a cooperative effect in vivo, but not in vitro, adds to the list of factors or conditions for which in vitro modulation of proliferation and migration is not necessarily predictive of in vivo effects on angiogenesis. (emphasis added)

Bussolino teaches that the observations were ***"surprising"***. In other words, Bussolino, one of skill in the art, did not find his results predictable. The data resulted in a ***"paradox"*** rather than an understanding. That is more experiments need to be done as conclusions cannot be drawn from the results presented in the reference. The reference provides an invitation to further experimentation rather than firm conclusions.

When the Bussolino reference is taken as a whole, per the author, no conclusion can be reached other than more experiments must be done. Bussolino does not provide a reasonable expectation as to how further experiments using his combination of growth factors and cytokines

will result, never mind how other combinations will result. Such an equivocal reference cannot provide a motivation to modify another reference. Therefore, withdrawal of the rejection is proper.

However, the Office Action specifically points to the one result that allegedly shows a synergistic effect of G-CSF and bFGF in inducing angiogenesis. The Office Action points to the abstract and methods. It is noted that the abstract does not state that a synergistic effect was observed, but instead that doses of each agent insufficient to promote angiogenesis alone were able to induce angiogenesis together in a rabbit corneal model. The discussion states that "we observed responses whose intensity is suggestive of a cooperative interaction of the two cytokines during angiogenesis," therefore, the interaction is likely only additive, at best.

The results of the corneal pellet assay of Bussolino provides a ***high and local concentration*** of G-CSF and bFGF in the pellets. The combination of the agents *in vitro* ***did not result in synergistic action of the agents despite multiple attempts*** as noted above. At best, an additive effect, which is the minimum that would be required to make the combination of the agents obvious, was observed.

The newly added claims 73-75 require systemic administration of GM-CSF. Isner specifically teaches administration of angiogenic agents to ischemic tissue to provide a ***local and high concentration***. Bussolino teaches that the cooperative action of angiogenic factors is variable, but that cooperative action is observed only when the factors are present at a ***local and high concentration***. Neither reference provides any teaching or suggestion to administer one or more angiogenic agents systemically. Moreover, both references teach that success from systemic administration is unlikely, at best.

Withdrawal of the rejection for obviousness is requested.

Double Patenting Rejections

Claims 49-59, 65, and 68-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 69-70 of co-pending U.S. Application No. 10/696,391.

Claims 49-61, 63-66, 68-70, and 72 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49, 52, 54-56, 58-65, and 68 of co-pending U.S. Application No. 10/696,391.

Applicants submit that upon consideration and entry of the instant Amendment and Response, the provisional double patenting rejections will be the only rejections remaining in the instant application. Therefore, pursuant to M.P.E.P. §822.01, Applicants respectfully request that the provisional obviousness-type double patent application be withdrawn so that the instant application may proceed to allowance.

The undersigned requests any extension of time necessary for response. The Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 47624DVC(71417).

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